

REMARKS

In the Office Action dated March 9, 2004, Claims 1-20 are pending. The Examiner has made the Restriction Requirement final. Consequently, Claims 4-8 and 10-11 are withdrawn from further consideration as drawn to non-elected subject matter. Claims 1-3, 9 and 12-20, drawn to a genetically modified animal or avian species having reduced levels of Bcl-w protein, are under consideration on the merits. The Description of the Drawings in the specification has been objected to for certain alleged informalities. Claims 1-3, 9 and 14-20 have been objected to as containing subject matter drawn to non-elected subject matter. Claim 20 has been objected to for a typographical error. Claims 1-3, 9, 12-13 and 18-20 have been rejected under 35 U.S.C. §101 as allegedly directed to non-statutory subject matter. Claims 1-3, 9 and 12-20 have been rejected under 35 U.S.C. §112, first paragraph, as allegedly lacking descriptive support. Claims 1-3, 9 and 12-20 have been rejected under 35 U.S.C. §112, first paragraph, as allegedly lacking enablement. Claims 1-3, 9 and 12-20 have been rejected under 35 U.S.C. §112, second paragraph, as allegedly indefinite.

This Response addresses each of the Examiner's rejections and objections. Applicants therefore respectfully submit that the present application is in condition for allowance. Favorable consideration of all pending claims is therefore respectfully requested.

In the first instance, Applicants have cancelled non-elected Claims 4-8 and 10-11, without prejudice. Applicants reserve the right to file a divisional application directed to the subject matter of such non-elected claims.

The Description of the Drawings in the specification has been objected to for certain alleged informalities. In response, Applicants have amended the specification in accordance with

the Examiner's suggestion. Therefore, the objection is obviated and withdrawal thereof is respectfully requested.

Claims 1-3, 9 and 14-20 have been objected to as containing subject matter drawn to non-elected subject matter. Claim 20 has been further objected to for a typographical error.

Claims 2 and 19 have been cancelled, without prejudice. Applicants have amended Claims 1, 3, 9, 14-18 and 20. In response, Applicants respectfully submit that Claims 1-3, 9 and 14-20, as amended, do not encompass non-elected subject matter, i.e., SEQ ID NO: 1, SEQ ID NO: 2, and a protein or gene associated with the human Bcl-w protein or the *bcl-w* gene. Claim 20, as amended, recites the correct spelling of the word "stringency." Accordingly, the objection of Claims 1-3, 9 and 14-20 is obviated and withdrawal thereof is respectfully requested.

Claims 1-3, 9, 12-13 and 18-20 have been rejected under 35 U.S.C. §101 as allegedly directed to non-statutory subject matter. The Examiner indicates that the claims encompass transgenic humans, which are not patentable.

In response, Applicants have cancelled Claims 2 and 19 and amended Claims 1, 3, 9, 12-13, 18 and 20 to recite "male non-human animal or avian species." Support for the amendment can be found throughout the specification, e.g., at page 10, lines 13-17 and page 24, line 5 to page 25, line 6.

Therefore, Claims 1-3, 9, 12-13 and 18-20, as amended, do not encompass humans. Accordingly, the rejection of Claims 1-3, 9, 12-13 and 18-20 under 35 U.S.C. §101 is overcome and withdrawal thereof is respectfully requested.

Claims 1-3, 9 and 12-20 have been rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the written description requirement.

The Examiner acknowledges that the specification has adequately described the nucleotide sequence set forth in SEQ ID NO: 3 and the nucleotide sequence encoding the amino acid sequence set forth in SEQ ID NO: 4. However, the Examiner contends that the specification does not describe any variant sequences within the claimed genus that encompasses nucleotide sequences having at least 47% similarity to the nucleotide sequence set forth in SEQ ID NO: 3, nucleotide sequences encoding an amino acid sequence having at least 47% similarity to SEQ ID NO: 4, nucleotide sequences capable of hybridizing to the nucleotide sequence set forth in SEQ ID NO: 3, or any nucleotide sequence encoding a Bcl-w protein. The Examiner also contends that it was unknown, as of Applicants' effective filing date, that any of these DNA molecules within the claimed genus would have the property of encoding a Bcl-w polypeptide having the same structural and functional properties as that encoded by SEQ ID NO: 3.

In response, Applicants respectfully submit that the present application adequately describes nucleotide sequences having at least 47% similarity to the nucleotide sequence set forth in SEQ ID NO: 3, nucleotide sequences encoding an amino acid sequence having at least 47% similarity to SEQ ID NO: 4, nucleotide sequences capable of hybridizing to the nucleotide sequence set forth in SEQ ID NO: 3, or any nucleotide sequence encoding a Bcl-w protein. For example, the present application teaches that Bcl-w belongs to pro-survival member of the Bcl-2 family. See, e.g., the specification, page 26, lines 19-21. Bcl-2 and many members in the Bcl2 family are well described in the art. See, e.g. Background of the Invention. The present application also specifically teaches that male mice with a disrupted portion of bcl-w gene fail to undergo productive spermatogenesis. See, e.g., page 3, lines 1-6 and Example 10 of the specification. Notably, Bcl-w is a pro-survival protein identified by the present inventors in

International Patent Application No. PCT/AU97/00199, which was published on October 2, 1997 as WO97/35971. The present application incorporates WO97/35971 by reference. See page 2, lines 24-26 of the specification. WO97/35971 literally describes nucleotide sequences similar to mouse bcl-w gene sequence (i.e., SEQ ID NO: 3 of the present application) which encodes an amino acid sequence having at least 47% similarity to mouse Bcl-w protein (SEQ ID NO: 4 of the present application). See page 5, lines 16-23 of WO97/35971. WO97/35971 also describes amino acid sequences having at least 47% similarity to SEQ ID NO: 4 (i.e., SEQ ID NO: 9 of WO97/35971). See page 3, lines 7-11 of WO97/35971. WO97/35971 further describes nucleotide sequences capable of hybridizing to the nucleotide sequence set forth in SEQ ID NO: 3 under low stringency and which encodes SEQ ID NO: 4 or any amino acid sequence having 47% or greater similarity to SEQ ID NO: 4. See, e.g., page 5, line 25 to page 6, line 5 of WO97/35971.

Therefore, Applicants respectfully submit that the nucleic acid and amino acid sequences, as recited in the present claims, are adequately described to those skilled in the art. The present application conveys to one skilled in the art that Applicants were in possession of the claimed invention at the relevant time. In this connection, Applicants respectfully submit that the Patent Office explicitly rejected a suggestion that requires a description to show physical possession. See Guidelines for Examination of Patent Applications Under the 35 U.S.C. § 112, ¶1, "Written Description" Requirement, *Federal Register*, Vol. 66, No. 4, Jan. 5, 2001, page 1101, third col. The Patent Office specifically pointed out, citing Ralston Purina Co. v Far-Mar-Co, Inc., 772 F.2d 1570, 1576, 227 USPQ 177, 180 (Fed. Cir. 1985), that "disclosure taken with the knowledge of those skilled in the art may be sufficient support for claims." *Id.* As described

above, the present application teaches that Bcl-w was found to be a pro-survival member of the Bcl-2 family. Two bcl-w genes, from human and mouse, were isolated and their nucleotide and amino acid sequences are provided by the present invention. The present invention also describes the function of Bcl-w protein. The present invention also specifically describes that mice having the disruption of a portion of the bcl-w gene fail to undergo spermatogenesis. The present invention further provides that a genetically modified male non-human animal comprising Bcl-w or a derivative or homologue thereof exhibits a reduced level of Bcl-w and thereby has an incapacity or reduced capacity to undergo spermatogenesis. As described above, a derivative or homologue of Bcl-w encompassed by the present invention comprises an amino acid sequence encoded by a nucleotide sequences having at least 47% similarity to the nucleotide sequence set forth in SEQ ID NO: 3; or a nucleotide sequence encoding an amino acid sequence having at least 47% similarity to SEQ ID NO: 4; or a nucleotide sequence capable of hybridizing to the nucleotide sequence set forth in SEQ ID NO: 3 under low stringency; or any nucleotide sequence encoding a Bcl-w protein. Methods for generating mutations or isolating derivatives and homologous are well established in the art. See, e.g., Sambrook et al., *Molecular Cloning*, CSHL Press, 1989. Thus, the disclosure of the present application taken with the knowledge in the art would permit one skilled in the art immediately to envisage the nucleotide and amino acid sequences claimed in the present application.

Moreover, in an effort to favorably advance the prosecution, Applicants have cancelled Claims 2 and 19, without prejudice, and amended Claims 1 to recite "wherein said Bcl-w protein comprises an amino acid sequence set forth in SEQ ID NO: 4 or is an amino acid sequence having at least about 47% similarity thereto." Claim 3 depends on Claim 1 and further

delineates that *Bcl-w* is encoded by SEQ ID NO: 3 or a nucleotide sequence having at least 47% identity thereto or a nucleotide sequence capable of hybridizing SEQ ID NO: 3 under low stringency conditions of 42°C. Similar amendment has been made to 12, 18 and 20. Claim 9 is amended to depend on Claims 1 and 3. Claim 13 depends on Claim 12.

Accordingly, Applicants respectfully submit that the rejection of Claims 1-3, 9 and 12-20 under 35 U.S.C. §112, first paragraph, is overcome and withdrawal thereof is respectfully requested.

Claims 1-3, 9 and 12-20 have been rejected under 35 U.S.C. §112, first paragraph, as allegedly lacking enablement.

The Examiner acknowledges that the specification is enabling for a transgenic male mouse whose genome comprises a homozygous disruption in the nucleotide sequence encoding *Bcl-w* as set forth by SEQ ID NO: 3, wherein the mouse exhibits an incapacity for spermatogenesis. However, the Examiner alleges that the specification is not enabling for other animals encompassed by the claims. Further, the Examiner contends that the specification does not teach any phenotype for any mouse other than homozygous males. Respecting homozygous male mice, the Examiner is of the opinion that the specification only teaches the phenotype of incapacity for spermatogenesis, not a reduced capacity for spermatogenesis. Moreover, the Examiner contends that the specification does not teach disruption of any gene other than that set forth by SEQ ID NO: 3. Additionally, the Examiner contends that the specification does not teach any type of genetic modification of the *Bcl-w* gene set forth by SEQ ID NO: 3. The Examiner also indicates that the art at the time of filing reported that the phenotype of transgenic knockout mice was unpredictable. Therefore, with respect to claims 12-17, which do not recite

any phenotype, the Examiner states that those skilled in the art cannot determine whether they have obtained the claimed animal. The Examiner further indicates that claims 1-3, 9 and 12-20 encompass a chimeric mouse (genetic mosaics) wherein only a portion of the cells of the mouse contains the claimed genetic disruption. The Examiner is of the opinion that it would take undue experimentation for those skilled in the art to determine the phenotype of a chimeric mouse. Finally, the Examiner indicates that claim 19, drawn to an animal comprising a mutation on chromosome 14q11, is not enabled, as 14q11 is the location of the human *Bcl-w* gene.

In the first instance, Applicants have cancelled Claims 2 and 19, without prejudice. In addition, Applicants have amended Claims 1, 3, 9 and 12-18 and 20 to delineate the claimed sequences as set forth in SEQ ID NO: 3 or 4 or sequences having 47% or greater similarity thereof or sequences that can hybridize to SEQ ID NO: 3 under low stringency condition. Claim 12 has been further amended to recite phenotype of the claimed animal.

Applicants observe that the specification describes that female mice homozygous for a deletion of the *Bcl-w* gene are fertile and *bcl-w*^{+/-} heterozygous mice phenotypes as normal mice. See page13, line 27 and Example 10 starting at page 22.

Applicants also observe that the present application provides a definition of "mutation" and how to generate a mutation that results in no active or substantially reduced levels of *Bcl-w* protein produced. See, e.g., page 14, lines 9-18. One skilled in the art, based on the teaching of the present invention, combined with techniques well established in the art, can readily make and use transgenic animals with a mutant *bcl-w* gene resulting in a reduced capacity for spermatogenesis. Applicants submit that those skilled in the art can also determine whether

a transgenic animal contains the desirable genetic modification by examining the genetic constituency of the animal, independent of any phenotype the animal may have.

Moreover, "[t]he omission of minor details does not cause a specification to fail to meet the enablement requirement." Genentech, Inc. v. Novo Nordisk, 108 F.3d 1361, 1366, 42 USPQ2d 1001, 1005 (Fed. Cir. 1997), cert. denied, 522 U.S. 963 (1997). A specification only needs to "supply the novel aspects of an invention in order to constitute adequate enablement." Id. (Emphasis added.) Thus, based on the teaching of the present application, those skilled in the art can make a transgenic animal as claimed and use such in the claimed method; and can also determine whether an animal contains the desirable genetic modification, without undue experimentation.

Therefore, the rejection of Claims 1-3, 9 and 12-20 under 35 U.S.C. §112, first paragraph, is overcome and withdrawal thereof is respectfully requested.

Claims 1-3, 9 and 12-20 have been rejected under 35 U.S.C. §112, second paragraph, as allegedly indefinite.

The Examiner alleges that the term "and/or" renders Claim 1 unclear. Applicants submit that Claim 1, as amended, does not recite "and/or" and is thus not indefinite.

The Examiner alleges that it is not clear as to whether the phrase "derivative or homologue thereof" refers to the Bcl-w protein or the protein associated with Bcl-w or both. Applicants submit that Claim 1, as amended, does not recite "the protein associated with Bcl-w." Thus, it is clear the phrase "derivative or homologue thereof" refers to the Bcl-w protein.

The Examiner alleges that the phrase "induce or facilitate" renders Claim 1 unclear. Applicants submit that the claims, as amended, replace "induce or facilitate" with "undergo" and

therefore obviate the objection. Support of the amendment can be found, e.g., on page 3, lines 1-6 of the specification.

The Examiner indicates that the term "reduced capacity" in claim 1 is a relative term, which renders the claim indefinite. Applicants respectfully submit that it is clear to those skilled in the art that the capacity is "reduced" when compared to an animal without the genetic modification affecting the level of the Bcl-w protein. However, in an effort to favorably advance the prosecution, Applicants have amended Claim 1 to recite "when compared to wild type male non-human animal or avian species."

The Examiner also alleges that claims 2, 3, and 12 are unclear for reciting "at least about". In response, Applicants respectfully submit that the meaning of the term is clear to those skilled in the art. Applicants further submit that the terms "at least" and "about" are both acceptable under the law. See, e.g., Ex parte Eastwood, 163 USPQ 316 (Bd. App. 1968).

The Examiner alleges that the phrase "capable of" in Claim 3 and 12 is a relative phrase and renders the claims indefinite. Applicants submit that Claim 3 and 12, as amended, do not recite "capable of" and are not indefinite.

The Examiner alleges that Claim 3 is unclear because it recites "a nucleotide sequence having at least about 47% similarity thereto." The Examiner alleges that only peptides share similarity and nucleotides share identity.

Applicants respectfully submit that the term "similarity" as defined on page 9, lines 3-17 of the specification encompasses exact identity between compared nucleotide sequences. However, in an effort to favorably advance the prosecution, Applicants have amended the claim to recite "a nucleotide sequence having at least about 47% identity thereto."

Furthermore, the Examiner alleges that the term "substantially" recited in claim 3, 12, 14, and 20 render the claims indefinite. In response, Applicants have deleted the term "substantially" from claims 3, 12 and 20. As to claim 14, Applicants submit that one skilled in the art clearly understands the metes and bounds of the recitation "substantially incapable of producing Bcl-w" under the law. For example, the court held that the limitation "to substantially increase the efficiency of the compound as a copper extractant" was definite in view of the general guidelines in the specification. In re Mattison, 509 F.2d 563, 184 USPQ 484 (CCPA 1975).

The Examiner alleges that Claim 16 is unclear, which seems to state that an antisense molecule can encode an antisense molecule. Applicants submit that Claim 16, as presently amended, is clear, which recites that a genetic sequence is an antisense molecule or encodes an antisense molecule.

The Examiner states that there is insufficient antecedent basis for the limitation "the Cre recombinase" in Claim 17. Applicants have amended Claim 17 to recite "a Cre recombinase."

The Examiner alleges that it is unclear as to whether the Cre gene of Claim 17 is part of the gene introduced into the bcl-w gene or is a second, independent genetic sequence. In response, Applicants have amended Claim 17 to recite that the gene introduced "is bounded by sites that permit excision of the region between said sites by the action of a Cre recombinase."

Accordingly, Claims 1-3, 9 and 12-20 are definite and clear. The rejection of Claims 1-3, 9 and 12-20 under 35 U.S.C. §112, second paragraph, is overcome and withdrawal thereof is respectfully requested.

In view of the foregoing amendments and remarks, it is firmly believed that the subject application is in condition for allowance, which action is earnestly solicited.

Respectfully submitted,

A handwritten signature in black ink, appearing to read 'F. S. DiGiglio', written in a cursive style.

Frank S. DiGiglio
Registration No. 31,346

SCULLY, SCOTT, MURPHY & PRESSER
400 Garden City Plaza
Garden City, New York 11530
(516) 742-4343

FSD/XZ/ZY:ab